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09/678,953	10/03/2000	Hiroshi Kubota	320727.50401.	7343

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EXAMINER	
SGAGIAS, MAGDALENE K	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/678,953	KUBOTA ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,14,27-37 and 41-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,14,27-37 and 41-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *1/30/06*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/24/06 has been entered.

Claims 1, 14, 27-37 and 41-55 are pending.

Claims 1, 14, 27-37 and 41-55 are under consideration.

Claim Objections

2. Claims 1, 27, 29, 41 and 49 are objected to because of the following informalities:

Claim 41 is depended from claim 40 wherein claim 40 has been canceled. Appropriate correction is required.

Claims 1, 27, 29 and 49 on step (c) recite the term "cytomerter". The term is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st Paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 14, 25-37, 41-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to an isolated single-cell bipotent hepatic progenitor or hepatic progenitor/composition which expresses at least one intercellular adhesion molecule (ICAM) antigen, does not express major histocompatibility complex (MHC) class Ia antigen, express at least one of CD44H, alpha-fetoprotein, albumin or CK19 or dull expression of a nonclassical MHC Ia antigen or higher side scatter (SSC) relative to non-parenchymal cells as measured by flow cytometry wherein said cell has the capacity to differentiate into a hepatocyte or a biliary cell when exposed to differentiation-inducing growth conditions. In further embodiments the claims are directed to hepatic progenitor cells/ composition which further express at least one MHC class Ib antigen or ICAM-1 or said cells/composition give rise to progeny and further embodiments require clonal growth of said cells/composition under extracellular matrix and further under feeder cells culture conditions. In further embodiments the cells are derived from endoderm such as liver, pancreas, lung, gut, thyroid, gonads or combinations thereof or bone marrow. While the specification provides teachings pertaining to production of hepatic progenitor cells from fetal rat livers wherein said cells are negative for MHC class Ia, dull for expression of MHC class Ib and positive for ICAM-1 expression and further said cells differentiate into biliary cell lineage in a matrigel culture system and a feeder cell culture system (specification p 14, 16, 20, p 24 and example 6.6, and p 27 examples 6.10 and 6.11), the specification fails to provide any relevant teachings or specific guidance or working examples with regard to the production of a single-cell bipotent hepatic progenitor and its progeny by way of the claimed invention. It appears that the guidance provided by the instant specification fails

to correlate the production of a single-cell bipotent hepatic progenitor cell by way of claimed method and its progeny expressing claimed cell surface markers wherein said cell is derived from tissues from a broad range of animal species including human. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed methods for the production of a single-cell bipotent hepatic progenitor cell expressing claimed cell surface markers and the production of its progeny. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

In determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are; the breadth of the claims, the nature of the invention, the state of the art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

These factors are analyzed, in turn, and demonstrate that one of ordinary skill in the art will need to perform "undue experimentation" to make and/or use the invention and therefore,

applicant's claims are not enabled.

The claims are directed to an isolated single-cell bipotent hepatic progenitor or hepatic progenitor cell expressing claimed cell surface markers wherein said cell has the capacity to differentiate into a hepatocyte or a biliary cell when exposed to differentiation-inducing growth conditions. While the specification provides teachings for the preparation and isolation of rat fetal progenitor hepatic cells which are $RT1A^{1-}OX18^{dull}ICAM\text{-}1^{+}$ and can form CK19 positive colonies in vitro (specification p 14-24), the specification has failed to provide guidance and/or working examples pertaining to an isolated single-cell bipotent hepatic progenitor cell which has the capacity to differentiate into a hepatocyte or a biliary cell by way of the claimed invention. Since the instant specification has failed to provide specific guidance or working examples correlating to an isolated single-cell bipotent hepatic progenitor cell which has the capacity to differentiate into a hepatocyte or a biliary cell one of skill in the art could not rely on the state of the isolation of a single-cell bipotent hepatic progenitor cell art to derive said cells by way of the claimed methods. This is because the art of isolating a single-cell bipotent hepatic progenitor from all animal species including human and their tissues is an unpredictable art with respect to hepatic progenitor cell existence and origin and ex vivo culture system of liver progenitor cells. Even after the filing date of the instant application **Zhang et al,** while reviewing the state of the art of bipotential hepatic cell existence and origin, noted that the question arises whether either or both of the cell lineages derived from the hepatoblast retain the "bipotential capacity" of the precursor cells (Zhang et al, World J Gastroenterol, 9(2): 201-204, 2003) (p 201, 2nd column under Hepatic Stem Cells in Canal of Hering). Zhang et al, reports also that in rodents, the concept of the bipotential cell, is now accepted however, the existence of a human equivalent remains controversial (p 201 2nd column, p 202 1st column). At the time of the instant invention **Baumann et al,** (Hepatology, 30:112-117, 1999) reports that while in rodents the concept of the

bipotential cell, the so called oval cell, is now accepted, the existence of a human equivalent remains controversial (p 112, 2nd column). There are now several independent reports describing cells in a number of human liver diseases with distinctive morphological or phenotypic features that resemble those characteristic of rodent progenitor cells however, questions regarding the cellular lineages of these putative cells remain open and will be difficult to resolve by immunohistochemical means alone (p 116, 2nd column). There are also reports of the isolation and long term culture of bipotent hepatoblasts however, bipotency is progressively lost during development and remains in only 5% of the liver cells at birth and whether there are progenitor cells taking part in adult liver homeostasis remains disputed (**Li et al,** Stem Cells, 24: 322-332, 2006) (p 322, 2nd column under Introduction). Li et al, also reports that despite the intensive studies on liver progenitor cells derived from rats, equivalent progenitor cells derived from mice are relatively rare ((abstract). Furthermore, Li et al, reports that bipotent hepatic progenitor so called oval cells is a name that only reflects their morphology: their origin, heterogeneity, and biologic roles remain ambiguous (p 330, 2nd column). **Petersen et al,** (Hepatology, 27: 433-445, 1998) states also that a number of problems must still be addressed such as understanding the mechanism involved in oval cell activation and develop a system to track these cells in vivo and to develop an in vitro system to understand their differentiation (p 444, 1st column). It appears from these reports that the isolation of bipotent hepatic progenitor cell populations or hepatic progenitor cell populations is still undeveloped and therefore the isolation of a corresponding singe-cell bipotent hepatic progenitor and its progeny from these populations is undeveloped. It appears that the state of the art is suggesting that the isolation of a singe-cell hepatic progenitor cell from all animal species including human might be feasible in the future. The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of isolating a single-cell bipotent hepatic

progenitor and its progeny from all animal species including human and their tissues raised by the state of the art. Therefore, the skilled artisan would conclude that the state of art of isolating a single-cell bipotent hepatic progenitor from all animal species including human and their tissues is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for isolating a single-cell bipotent hepatic progenitor from all animal species and their tissues without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the isolation of a single-cell bipotent hepatic progenitor or hepatic progenitor cell and particularly giving rise to its progeny, the lack of direction or guidance provided by the specification for the isolation of a single-cell bipotent hepatic progenitor or hepatic progenitor cell and particularly giving rise to its progeny, the absence of working examples that correlate to the isolation of a single-cell bipotent hepatic progenitor or hepatic progenitor cell and particularly giving rise to its progeny, the unpredictable state of the art with respect to the isolation of a single-cell bipotent hepatic progenitor or hepatic progenitor cell and particularly giving rise to its progeny, the undeveloped state of the art pertaining to the isolation of a single-cell bipotent hepatic progenitor or hepatic progenitor cell and particularly giving rise to its progeny, and the breadth of the claims directed to all animal species of said cells including human and its progeny, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Response to Arguments

5. Applicant's arguments filed on 2/24/06 have been fully considered but they are not persuasive. Applicants argue that claims 1, 14, 27-29, 42 and 49 have been amended.

Applicants argue that support for bipotent hepatic progenitors which exhibit at least one of the following characteristics: (1) expression of at least one of CD44H, alpha-fetoprotein, albumin or CK19, or (2) dull expression of a nonclassical human MHC class Ia antigen, or (3) higher side scatter (SSC) relative to non-parenchymal cells as measured in a flow cytometer may be found throughout the specification and in the flowchart under section 6.11 and at least at page 10, lines 27-8. .

Applicants further argue that they have amended the independent claims to recite at least one of the following characteristics of the claimed hepatic bipotent progenitor cells: (1) expression of at least one of CD44H, alpha-fetoprotein, albumin or CK19, or (2) dull expression of a nonclassical human MHC class Ia antigen, or (3) higher side scatter (SSC) relative to non-parenchymal cells as measured in a flow cytometer and independent claims now explicitly recite bipotent hepatic progenitors having the capacity to differentiate into hepatocytes or biliary cells.

Applicants maintain that the identification of cells based on expression of at least one ICAM antigen and lack of MHC class Ia antigen expression in conjunction with a selection step based on one additional recited characteristic (i.e. steps (iii) and (c) in claims 22 and 23 respectively) is indeed sufficient to isolate bipotent hepatic progenitors. Applicants also argue that this methodology is explicitly summarized on page 10, lines 10-13 and the flow chart under example 6.11 and paragraph 0079. Cell suspensions stained with anti-RTIA-specific for MHC class Ia and anti-ICAM-1and sorted into discrete cell populations identifiable according to their respective staining pattern wherein these populations then screened for clonal growth potential in vitro and for the presence of additional markers present on hepatic progenitor cells. Thus, Applicants submit that the instant claimed method is sufficient to uniquely identify bipotent hepatic progenitor cells and enable one of ordinary skill in the art to accomplish the same.

These arguments have been fully considered, but are not persuasive. Page 10 of the

specification, cited by Applicants, states that ICAM positive cells include hematopoietic, mesenchymal, and mature hepatic cells, and that MHC class I negative cells include bipotent hepatic progenitor cells, enucleated mature erythrocytes and an unidentified cell population. Thus, it is possible that, sorting cells by these two markers alone (expression of ICAM-1 and lack of MHC class I) could result in, for example, a hematopoietic cell, such as an erythrocyte, as erythrocytes are hematopoietic cells. It is also possible that the cells in the "unidentified cell population" are cells that are also ICAM positive cells, and that identification of the resultant cells would also have the instantly claimed characteristics. The flow chart, as pointed to by Applicant has more steps that result in merely sorting the cells by two markers, to result in bipotent hepatic progenitor cells. For example, there is a step to eliminate red blood cells, and further steps of isolation. The claimed invention is directed to a cell that expresses at least one ICAM antigen, and does not express MHC class Ia antigen and it is maintained that the recitation of these characteristics alone fails to attain the instant invention, which are bipotent hepatic progenitor cells. The specification teaches the isolation and identification of rat hepatic progenitor cells. The specification has not provided guidance and/or working examples for the isolation and identification of all species including human hepatic progenitor cells as embraced by the claims. At the time of the instant invention, the art of record teaches that there are no specific human cell surface markers that could be used to isolate and identify human hepatic progenitor cells (**Roskans et al,** Seminars in Liver Disease, 23(4): 385-96, 2003). Roskans et al, reports that at present, a major problem is the difficulty of isolating human liver progenitor cells, mainly because there is no specific progenitor cell marker (p 396, 1st column). Roskans et al, further discusses that, better comparison of human liver diseases with animal models of oval cell activation may establish which animal models are most representative for the human situation (p 396, 2nd column). Even the selection of cells based on expression of at least one

ICAM antigen and lack of MHC class Ia antigen expression in conjunction with a selection step based on one additional recited characteristic (i.e. steps (iii) and (c) in claims 22 and 23 respectively) is indeed insufficient to isolate and identify all animal species including human bipotent hepatic progenitors as the instant claims have been amended. This is because the art of isolating and identifying human hepatic progenitor cells from liver tissue is an unpredictable art with respect to human hepatic progenitor ex vivo culture system. At the time of the instant invention **Baumann et al,** (Hepatology, 30:112-117, 1999) reports that while in rodents the concept of the bipotential cell, the so-called oval cell, is accepted, the existence of human equivalent remains controversial (p 112, 2nd column). There are now several independent reports describing cells in a number of human liver diseases with distinctive morphological or phenotypic features that resemble those characteristic of rodent progenitor cells however, questions regarding the cellular lineages of these putative stem cells remain open and will be difficult to resolve by immunohistochemical means alone (Baumann et al, p 116, 2nd column). It appears that the state of the art is suggesting that at the time of the instant application the isolation and identification of human hepatic progenitor cells might be feasible in the future. In fact, after the filling date of the instant application, **Parent et al,** (Gastroenterology, 126(4): 1147-56, 2004) reports that they have developed HepaRG cells which constitute the first described human hepatic bipotent progenitor cell line regarding phenotype and histological origin by using immunofluorescence, immunoblotting, and flow cytometry (abstract). **Parent et al,** further notes that: "Up to now, no human liver oval cell line has been successfully established" (p 126, 2nd column under discussion). In addition, **Weber et al,** (Pathologie Biologie, 54: 58-63, 2006) while reviewing the art of primate hepatic foetal progenitor cells notes that the existence of an equivalent of oval cells in humans has been debated for a long time and it is now generally admitted that such progenitor cells exist in human liver and are activated in

liver diseases however, "a niche" of oval cells has never been identified in normal liver and there is no specific progenitor cell marker (p 59, 2nd column).

Furthermore, with regard to the cell surface markers, first, it is not clear how bipotent hepatic progenitors can be isolated from a hepatic cell suspension by virtue of the ICAM antigen and/or CD44H cell surface markers (see step (b) of claim 22). It is well known in the art that human liver tissue contains hematopoietic, mesenchymal and mature hepatic cells. The specification teaches also that hepatic cell populations that express ICAM-1 include hematopoietic, mesenchymal and mature hepatic cells. Thus, expression of an ICAM antigen to isolate hepatic progenitors from an hepatic cell suspension as embraced by the instant claims in conjunction with the expression of at least one of CD44H cell surface marker is critical to enable the claimed invention. In fact, the art teaches that human mesenchymal stem cells (MSCs) express ICAM-1 and CD44H (Conget et al, (Journal of Cellular Physiology, 181: 67-73, 1999). Therefore, the markers embraced by the claims are not correlative to hepatic progenitor cells. Second, it is not clear when removing from the hepatic cell suspension those cells that express at least one human MHC class Ia antigen (see step (b) (i) claim 22) is considered a bipotent hepatic progenitor-restricted cell surface marker. Third, it is not clear when isolating from a hepatic cell suspension those cells that, for example, express CK19 or alpha-fetoprotein is considered a hepatic progenitor cell surface marker (see step (b) (iii), claim 22). The art teaches that differentiated hepatocytes have also been stained for alpha-fetoprotein and CK19 of human fetal hepatocyte cultures (Lazaro et al, Hepatology, 38(5): 1095-1106, 2003) (p 1103, 2nd column). Fourth, it is not clear when isolating cells from a hepatic cell suspension those cells for dull expression of a non-classical human MHC class Ia antigen is considered a hepatic progenitor-restricted cell surface marker (see step (b) (iii) claim 22). The term dull is a relative term and it is not clear as to what is the threshold of dull expression as measured by flow

cytometry in the instant case. Fifth, it is not clear how to isolate a single-cell bipotent hepatic progenitor based on said cell surface markers by flow cytometry. It is known in the art that using flow cytometry the end product is a population of cells sorted based on their cell surface markers. Therefore, it is not clear as to how to isolate a single-cell bipotent hepatic progenitor which will have the capacity to differentiate into a hepatocyte or biliary cell when exposed to differentiation-inducing growth factors by way of the claimed invention. The instant specification does not provide any relevant teachings, specific guidance or working examples for overcoming the limitations of isolating and identifying human hepatic progenitor cells from a human liver tissue raised by the state of the art.

In light of the above recited art it appears that the isolation and identification of human hepatic progenitor cells at the time of the instant application is an accomplishment for the future. The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of isolating and identifying bipotent hepatic progenitor cells from human liver tissue raised by the state of the art. Therefore, the skilled artisan would conclude that the state of art of isolating and identifying human hepatic progenitor from human liver tissue is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for isolating and identifying human hepatic progenitor cells from human liver tissue without a reasonable expectation of success.

Thus, it is maintained that the lack expression of MHC class I and expression of ICAM in conjunction with the added panel of cell surface markers as per amended claims are not sufficient to uniquely isolate and identify bipotent hepatic progenitor cells. Note further that MHC has three alleles, which are expressed throughout the population, thus, the lack of expression of class Ia may not, in itself, be sufficient to uniquely identify the bipotent hepatic

progenitor cells. In view of the lack of teaching or guidance provided by the specification with regard to utilizing only particular markers to identify the bipotent hepatic progenitor cells, the teachings in the art to show that cells other than bipotent hepatic progenitor cells express the claimed markers, it would have required undue experimentation for one of skill in the art to practice the claimed invention.

Conclusion

6. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla, can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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